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(71) Applicant (for all designated States except US):
LEO PHARMACEUTICAL PRODUCTS LTD. A/S
(LØVENS KEMISKE FABRIK PRODUKTIONS-
TIESELSKAB) [DK/DK]; Industriparken 55, DK-2750
Ballerup (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HØY, Gert**
[DK/DK]; Stenkrogen 36, DK-4040 Jyllinge (DK).
DIDRIKSEN, Erik, Johannes [DK/DK]; Fuglehavevej
14, DK-2750 Ballerup (DK).

(74) Agent: **THALSØ-MADSEN, Birgit;** Head of Patent
Section, Leo Pharmaceutical Products, Industriparken 55,
DK-2750 Ballerup (DK).

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(54) Title: TOPICAL COMPOSITION CONTAINING AT LEAST ONE VITAMIN D OR ONE VITAMIN D ANALOGUE AND
AT LEAST ONE CORTICOSTEROID

(57) Abstract: The present invention relates to a pharmaceutical gel composition for application on skin, said composition compris-
ing at least one vitamin D or vitamin D analogue and at least one corticosteroid as well as a viscosity-increasing excipient.

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TOPICAL COMPOSITION CONTAINING AT LEAST ONE VITAMIN D OR ONE VITAMIN D
ANALOGUE AND AT LEAST ONE CORTICOSTEROID

FIELD OF THE INVENTION

- 5 The present invention concerns topical compositions for application on skin which contain at least one vitamin D or vitamin D analogue and at least one corticosteroid.

BACKGROUND OF THE INVENTION

- 10 In the treatment of a number of conditions using dermal application, e.g. in the treatment of psoriasis, it is often indicated to employ a combination treatment incorporating two or even more different pharmacologically active compounds. Thus, in the treatment of e.g. psoriasis, it is known to use a combination treatment involving a steroid compound, such as a corticosteroid compound, and a vitamin D analogue such as calcipotriol, and where
15 each of the active compounds are formulated in separate preparations due to the instability of corticosteroids at alkaline pH values and of vitamin D analogues at acid pH values.

- Consequently, physicians have had to resort to letting patients under this type of two-component regimen perform sequential application of two creams/ointments, each
20 containing one of the compounds formulated at its maximum stability pH. This may lead to incompatibility of the preparations so that patients must, e.g., apply one cream/ointment in the morning and the other in the evening. Needless to say, patient compliance as well as correct administration dosage is a problem under such circumstances. Richards, H.L. et al. report in *J Am Acad Dermatol* 1999 Oct; 41(4):581-3 on a study of patients with psoriasis
25 and their compliance with medication. They report that poor compliance with treatment advice in chronic conditions, such as psoriasis, represents a major challenge to health care professionals: Thirty-nine percent of participants reported that they did not comply with the treatment regimen recommended. The noncompliant group had a higher self-rated severity of psoriasis, were younger, and had a younger age at onset than those who were
30 compliant. The noncompliant group reported that psoriasis had a greater impact on daily life.

- WO 00/64450 describes a pharmaceutical composition for dermal use comprising a combination of a vitamin D analogue and a corticosteroid, which composition alleviates the
35 inconveniences of a two-component or multi-component regimen for the treatment of psoriasis and related skin diseases. This composition, however, tends to be rather oily and to leave, on application, a greasy film of non-absorbed excipients on the skin.

SUMMARY OF THE INVENTION

It is therefore the object of the present invention to provide a composition comprising both active components in a formulation exhibiting improved skin absorption (and less oily appearance) and ease of application, both qualities leading to improved patient compliance.

Accordingly, the present invention relates to a pharmaceutical gel composition for application on skin, said composition comprising at least one vitamin D or vitamin D analogue and at least one corticosteroid, said composition further comprising a viscosity-increasing excipient in an amount resulting in a viscosity which, on the one hand, is sufficient to substantially prevent the corticosteroid from sedimenting during application and storage of the composition and, on the other hand, is sufficient to facilitate an even distribution of the composition on an affected skin area.

The gel composition of the invention has been found to be particularly favourable for application on the scalp due to the ease with which it may be applied and to the considerably less oily appearance which makes the composition more acceptable to patients suffering from psoriasis of the scalp.

In another aspect, the invention relates to the use of a gel composition as defined above for the manufacture of a medicament for the topical treatment of psoriasis and related conditions, e.g. sebo-psoriasis of the scalp, in humans.

DETAILED DESCRIPTION OF THE INVENTION

In the present context, the term "sufficient", when used in connection with viscosity, is understood to indicate a viscosity which, on the one hand, is sufficiently high to ensure that the corticosteroid (which is present in the composition in the form of dispersed particles) does not sediment from the composition which would, of course, result in an uneven application of the corticosteroid over the affected area. On the other hand, the viscosity of the application should be sufficiently low to enable the patient to readily remove the required dose of the composition from the container in which it is available (e.g. a tube or the like) and apply it evenly over the affected area to ensure an even dosing of the active components.

For application of the present composition on the scalp, it is particularly important to ensure that the viscosity is sufficiently high to substantially prevent "leakage" of the composition from the area where it is applied to other areas, in particular the face. It is equally important that the composition is readily applied on an area of skin covered by hair to ensure correct dosing of the active components.

In practical terms, this means that the viscosity should preferably be in the range of from about 5 mPa.s to about 500 mPa.s, in particular from about 10 mPa.s to about 250 mPa.s, such as from about 20 mPa.s to about 100 mPa.s. The viscosity may suitably be determined by the cup/rotor method involving an NV1 device on a Haake VT 550 viscosimeter at 700 s^{-1} and 20°C .

In a currently favoured embodiment, a suitable viscosity of the composition may be obtained by including a thixotropic gelling agent as the viscosity-increasing excipient such that the composition, on standing, is in the form of a gel. A thixotropic agent has the advantage of being readily applied while, on standing, such as after application, the viscosity increases so that the composition will typically not leak from affected areas of skin on which it is applied to unaffected areas. An example of a suitable thixotropic gelling agent is hydrogenated castor oil.

In an alternative embodiment, the viscosity-increasing excipient may be selected from a wax, e.g. Cera Alba (white wax) or Cera Flava (yellow wax), polyethylene or a microcrystalline wax such as Esma-P®.

When the composition is an emulsion, it may be a water-in-oil or oil-in-water emulsion comprising a suitable emulsifier which may, for instance, be selected from polyoxyethylene cetyl ether, polyoxyethylene stearyl ether or polyoxyethylene oleyl ether, or polyethyleneglycol dipolyhydroxystearate.

In order to circumvent the problem of instability of certain vitamin D analogues in an acid environment (they have a maximum stability at pH values above about 8) and instability of corticosteroids in an alkaline environment (they have a maximum stability at a pH of about 4-6), it is furthermore preferred that the composition is substantially non-aqueous. The term "substantially non-aqueous" is intended to indicate that the composition has a water content below about 5%, preferably below about 2%, such as below about 1.5%.

Consequently, the composition preferably comprises at least one substantially non-aqueous solvent selected for its ability to dissolve or solubilise the vitamin D analogue. The solvent may suitably be selected from the group consisting of:

- (i) compounds of the general formula $R^3(OCH_2C(R^1)H)_xOR^2$ (I) wherein x is in the range of 2-60, R^1 in each of the x units independently is H or CH_3 , R^2 is straight chain or branched C_{1-20} alkyl or benzoyl, and R^3 is H or phenylcarbonyloxy;
- (ii) di-(straight or branched)- C_{4-10} alkyl esters of C_4-C_8 dicarboxylic acids;
- (iii) straight or branched C_{12-18} -alkyl benzoates;
- (iv) straight or branched C_{2-4} -alkyl esters of straight or branched C_{10-18} -alkanoic or -alkenolc acids;
- (v) propylenglycol diesters with C_{8-14} -alkanoic acids; and
- (vi) branched primary C_{18-24} alkanols.

It has been found that in such combination compositions containing a solvent selected from one of the group indicated above and in a substantially non-aqueous environment, the active components can co-exist without degradation, despite their different pH/stability profiles. The tendencies of the active compounds to affect one another with regard to pH is minimised or eliminated.

In the general formula (I) defined above, it is preferred that the factor x (which designates the number of the units within the parentheses) is in the range 4-50, more preferably 4-40, in particular 4-30, especially 5-25, more especially 10-20, such as about 15. It is further preferred that R^1 is CH_3 .

It is preferred that the solvent is selected from compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) where R^1 , x, and R^2 are as defined above, and mixtures thereof.

As non-limiting specific examples of the types (i)-(vi) of the solvent defined above may be mentioned the following, including trade names:

- Arlamol E (polyoxyethylene(15) stearyl ether);
- Arlamol DoA (diisooctyl ester of adipic acid);
- Arlasolve 200 (Polyoxyethylene-20-Isohexadecyl ether);
- Eutanol G (2-octyldodecanol);
- Finsolv (Isostearyl benzoate);
- Finsolv P (polyoxypropylene-15-stearyl ether benzoate);

Isopropylesters of straight or branched C₁₀ - C₁₈ alkanolic or alkenolic acids such as isopropyl myristate, isopropyl palmitate, isopropyl isostearate, isopropyl linolate and isopropyl monooleate;

Miglyol 840 (Propylene glycol diester of caprylic and caprinic acid);

5 DPPG (propylene glycol dipelargonate);

Procetyl AWS (CH₃(CH₂)₁₄CH₂(OCH(CH₃)CH₂)₅-(OCH₂)₂₀OH).

10 In the present context, the term "vitamin D analogue" is intended to indicate a synthetic compound comprising a vitamin D scaffold with sidechain modifications and/or modifications of the vitamin D scaffold itself. The term is not intended to include naturally occurring vitamin D derivatives such as metabolites.

15 The vitamin D analogue included in the present composition is preferably a compound selected from the group consisting of seocalcitol; calcipotriol; calcitriol; tacalcitol, maxacalcitol; paricalcitol; falecalcitriol; 1 α ,24S-dihydroxy-vitamin D₂; and 1(S),3(R)-dihydroxy-20(R)-[[(3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene, as well as mixtures thereof.

20 More preferred are vitamin D analogues selected from the group consisting of calcipotriol, calcitriol, tacalcitol, maxacalcitol, and 1(S),3(R)-dihydroxy-20(R)-[[(3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene as well as mixtures thereof. Synthetic vitamin D analogues are more preferred in the compositions according to the invention than naturally occurring vitamin D's or vitamin D derivatives, since the therapeutic effects of the latter may be less selective for the treatment of skin diseases, such as psoriasis.

Further non-limiting examples of vitamin D analogues are:

alphacalcidol;

1 α -hydroxy-vitamin D₂;

30 1 α -hydroxy-vitamin D₅;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6-hydroxy-6-methyl-1-heptyl)-9,10-secopregna-5(2),7(E)-10(19)-triene;

35 1(S),3(R)-Dihydroxy-20(R)-(6-hydroxy-6-methylhept-1(E)-ene-1-yl-9,10)-secopregna-5(Z),7(E),10(19)-triene;

- 1(S),3(R)-Dihydroxy-20(R)-(6-ethyl-6-hydroxy-1-octyl)-9,10)-secopregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(7-hydroxy-7-methyl-1-octyl)-9,10)-secopregna-5(2),7(E),10(19)-triene;
- 5 1(S),3(R)-Dihydroxy-20(R)-(7-hydroxy-7-methyloct-1(E)-en-1-yl-9,10)-secopregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(6'-methyl-1'-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(S)-(5'-hydroxy-5'-methyl-1'-hexyloxy)-9,10-secopregna-5(Z),7(E),10(19)-triene;
- 10 1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'-ethyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(6'-hydroxy-1'-hexyloxy-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 15 1(S),3(R)-Dihydroxy-20(R)-(5'-hydroxy-5'-ethyl-1'-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10,19-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(5'-hydroxy-5'-methyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(5'-methyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 20 1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'-(1"-propyl)-1'-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'-methyl-1'-pentyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 25 1(S),3(R)-Dihydroxy-20(R)-(3'-hydroxy-3'-methyl-1'-butyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-1-hept-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;
- 30 1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-hept-1(E)-en-1-yl),9,10-secopregna-5(2),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(2),7(E),10(19)-triene;
- 35 1(S),3(R)-Dihydroxy-20-(5'-ethyl-5'hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

- 1(S),3(R)-Dihydroxy-20-(6'-hydroxy-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z)-7(E),10,19-triene (5'(R) and 5'(S) isomers);
- 5 1(S),3(R)-Dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3''(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(3-(2-hydroxy-2-pentyl)-phenylmethoxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(3-(3-hydroxy-3-propyl)-phenylmethoxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 10 1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-methyl-1-pentyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-methyl-1-pent-2-ynyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 15 1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-trifluoromethyl-5,5,5-trifluoro-1-pent-2-ynyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-[3-(2-hydroxy-2-propyl)-phenoxy-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-[3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 20 1(S),3(R)-Dihydroxy-20(R)-[3-(2-hydroxy-2-propyl)-5-methylphenyl)-methoxy]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-[3-(2-hydroxy-2-propyl)-5-methoxyphenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 25 1(S),3(R)-Dihydroxy-20(R)-(3-hydroxy-3-ethyl-1-pentylthiomethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(3-hydroxy-3-ethyl-1-pentylsulphonylmethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(3-((1-hydroxy-1-methyl)ethyl)phenylthiomethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 30 1(S),3(R)-Dihydroxy-20(R)-(3,3-difluoro-4-hydroxy-4-methyl-1-pentyloxymethyl)-9,10-seco-pregna-5(Z)-7(E),10(19)-triene;
- 1(S),3(R)-Dihydroxy-20(R)-(6'-ethyl-6'-hydroxy-oct-1'-yn-1'-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;
- 35 1(S),3(R)-Dihydroxy-20(R)-(7'-ethyl-7'-hydroxy-non-1'-yn-1'-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

- 1(S),3(R)-Dihydroxy-20(R)-(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; Isomer A;
1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-methoxy-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; Isomer A;
- 5 1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; Isomer A;
1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-hydroxy-4-ethyl-2-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; Isomer A;
- 10 1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-ethyl-2-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; Isomer A;
1(S),3(R)-Dihydroxy-20-(4-ethyl-4-hydroxy-1-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19),17(20)(Z)-tetraene;
1(S),3(R)-Dihydroxy-20-(5-ethyl-5-hydroxy-1-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19),17(20)(Z)-tetraene;
- 15 1(S),3(R)-Dihydroxy-20-(6-ethyl-6-hydroxy-1-octyn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19),17(20)(Z)-tetraene;
1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-4,4-difluoro-5-hydroxy-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-(4,4-dichloro-5-hydroxy-5-methyl-hexyloxy)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;
- 20 1(S),3(R)-Dihydroxy-20(R)-(4,4-difluoro-5-hydroxy-5-methyl-hexyloxy)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-(4-fluoro-4-methyl-pentyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 25 1(S),3(R)-Dihydroxy-20(R)-(4-ethyl-4-fluoro-hexyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-(5-fluoro-5-methyl-hexyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 30 1(S),3(R),20(S)-Trihydroxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(S)-methoxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(S)-ethoxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;
- 35 1(S),3(R)-Dihydroxy-20(S)-[3-(2-hydroxy-2-methyl-1-propoxy)-prop-1E-en-1-yl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

- 1(S),3(R)-Dihydroxy-20(R)-(4-ethyl-4-hydroxy-1-hexylthio)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-[5-methyl-5-hydroxy-1-hexylthio]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 5 1(S),3(R)-Dihydroxy-20(R)-[3-(1-methyl-1-hydroxyethyl)benzylthio]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-(3-methyl-3-hydroxy-1-butylthio)-9,10-seco-pregna-5(Z)-7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-hept-1(E)-en-3-yn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 10 24-oxo-1(S),3(R),25-Trihydroxy-20(S)-9,10-seco-cholesta-5(Z),7(E),10,19-triene;
1(S),3(R)-Dihydroxy-20(R)-(3-oxo-4-hydroxy-4-ethyl-1-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20-methyl-18-(5-methyl-5-hydroxy-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 15 1(S),3(R)-Dihydroxy-20-methyl-18-(4-ethyl-4-hydroxy-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20-methyl-18-(4-ethyl-4-hydroxy-hex-2-ynyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 20 1(S),3(R)-Dihydroxy-20-methyl-18-(4-hydroxy-4-methylpentyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20-methyl-18-(4-hydroxy-4-methylpent)-2-yn-1-yloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20-methyl-18-(3,1-hydroxy-1-methylethyl)phenylmethyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
- 25 1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-hydroxy-4-methyl-1-pentyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A;
1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-methyl-1-pentyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A;
- 30 1(S),3(R),25-Trihydroxy-(20(S)-9,10-seco-cholesta-5(Z),7(E),10(19),23(E)-tetraene;
1(S),3(R)-Dihydroxy-(20(S)-(6'-hydroxy-6'-methyl-4'(E)-hepten-1'yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;
1(S),3(R),22(S),25-Tetrahydroxy-20(R),9,10-seco-cholesta-5(Z),7(E),10(19),23(E)-tetraene;
- 35 22(S)-Ethoxy-1(S)-3(R),25-trihydroxy-10(R)-,9,10-seco-cholesta-5(Z),7(E),10(1,23(E)-tetraene;

1(S),3(R)-Dihydroxy-20(S)-(3-(1-hydroxy-1-methylethyl)phenoxyethyl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(R) isomer;

1(S),3(R)-Dihydroxy-20(S)-(3-(1-hydroxy-1-methylethyl)phenylthiomethyl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(R) isomer;

5 1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-4-methylpent-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxyhept-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(S) isomer;

10 1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxyhepta-1(E),3(E)-dien-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(S) isomer;

1(S),3(R)-Dihydroxy-20(R)-(3-cyclopropyl-3-hydroxyprop-1(E)-en-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene (24(S) isomer) or the corresponding 24(R) isomer; and

1(S),3(R)-Dihydroxy-20(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, both 22-isomers.

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The corticosteroid may be a group I, II, III or IV topical steroid. The corticosteroid is preferably selected from the group consisting of Betamethasone (9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione) and esters thereof such as the 21-acetate, 17-adamantoate, 17-benzoate, 17-valerate, and 17,21-dipropionate;

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Alclomethasone and esters thereof such as the dipropionate; Clobetasole and esters thereof such as the propionate; Clobetasone and esters thereof such as the 17-butyrate; Desoximetasone; Diflucortolon and esters thereof, Diflorasone and esters thereof such as the diacetate; Fluocinonid; Flumetasone and esters thereof such as the pivalate;

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Fluocinolone and ethers and esters thereof such as the acetonide; Fluticasone and esters thereof such as the propionate; Fluprednidene and esters thereof such as the acetate; Halcinonide; Hydrocortisone and esters thereof such as the -17-butyrate; Mometasone and esters thereof such as the furoate; and Triamcinolone and ethers and esters thereof such as the acetonide; as well as mixtures thereof. More preferred examples of the corticosteroids are Betamethasone or esters thereof such as the 17-valerate or the 17,21-dipropionate,

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Clobetasole or esters thereof such as the propionate, Triamcinolone or ethers and/or thereof such as the acetonide or the acetonide-21-N-benzoyl-2-methyl- β -alaninate or the acetonide-21-(3,3-dimethylbutyrate), or Hydrocortisone or esters thereof such as the 17-butyrate.

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The composition of the present invention may be prepared in accordance with methods well known to the person skilled in the field of pharmaceutical formulation. Thus, the non-aqueous compositions may be prepared by incorporating the components into a well known

ointment or lotion base excipient such as liquid paraffin or Plastibase™ (a base prepared from polyethylene (average MW about 21,000) and paraffin liquid) or ESMA-PTM (a microcrystalline wax). It is, however, generally preferred to select an ointment or lotion base excipient which, on application, imparts to skin, hair and scalp a less oily appearance than does liquid paraffin, such as for instance heptamethylnonane.

As an example, preparation of a composition according to the invention is typically performed by melting the base excipient (e.g. heptamethylnonane and/or hydrogenated castor oil), adding a solution (typically at a concentration in the range of 0.0005-2.5% w/w) of the vitamin D analogue in the required amount of solvent, e.g. Arlamol® E, followed by addition of a dispersion of the corticosteroid in base excipient, typically with a particle size of from 0.1 to 20 µm, and then cooling the mixture. Typical content ranges of the various components in the finished composition according to the invention are from about 0.005 to about 0.3% w/w, preferably 0.01-0.2% w/w, of the corticosteroid, from about 0.0001 to about 0.035% w/w of the vitamin D analogue, from about 0.1 to about 25% w/w, preferably about 0.5-10% w/w, of the viscosity-increasing agent, optionally from about 0.5 to about 10 % w/w of the surfactant, and from about 1 to about 30% w/w of the solvent, the remainder typically being primarily base excipient such as the above-mentioned heptamethylnonane. The composition may also contain other commonly used additives such as antioxidants (e.g. α-tocopherol).

In a particular embodiment intended for application on the scalp, the present composition may additionally comprise a surfactant. This may be an advantage in cases where it is intended to apply the composition and leave it on the scalp for a sufficient period of time to ensure that the active components are absorbed in the skin of the scalp after which the remainder of the composition may be washed away to give the hair a "clean" (non-oily) appearance. The surfactant may be selected from fatty esters of a type generally considered suitable for application on the scalp, e.g. sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate or polyoxyethylene sorbitan monooleate. However, some vitamin D analogues tend to be degraded in the presence of even small amounts of free fatty acids found as impurities in esters. Preferred surfactants for inclusion in compositions comprising such vitamin D analogues are therefore ethers, e.g. ethers selected from the group consisting of octoxynol-n of formula $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$, wherein n is an integer of from 1 to 70, nonoxynol-n of formula $C_9H_{19}C_6H_4(OCH_2CH_2)_pOH$, wherein p is an integer of

from 4 to 40, and a polyoxyethylene C₁₂₋₂₂ alkyl ether, e.g. polyoxyethylene lauryl ether, polyoxyethylene cetyl ether, polyoxyethylene stearyl ether or polyoxyethylene oleyl ether.

The resulting composition may conveniently be filled into an appropriate container, e.g. a metal or plastic tube, a bottle, or a dispenser provided with suitable means to measure a correct dose of the composition.

The composition of the invention may further comprise an anti-fungal agent which is, e.g., selected from the group consisting of miconazol, clotrimazol, terbinafin, ciclopirox, bifonazol, nystatin, ketoconazol, econazol, and fluconazol.

Preferably, the compositions according to the invention do not contain therapeutically effective compounds selected from the group consisting of the xanthine derivatives pentoxifylline, propentofyllin, and torbafylline, or any other xanthine or xanthine derivative.

The invention also relates to a method of treatment of psoriasis and related skin diseases, e.g. sebo-psoriasis of the scalp, comprising topically administering an effective amount of a composition according to the invention to a patient in need of such treatment. Said method preferably comprises topical administration once or twice a day of a therapeutically sufficient dosage of said composition. The composition according to the invention preferably contains about 0.001-0.5mg/g or ml, preferably about 0.001-0.25mg/g or ml, of the vitamin D or vitamin D analogue, and about 0.05-2 mg/g or ml, preferably about 0.1-1.5 mg/g or ml, of the corticosteroid.

The invention is further illustrated by the following examples which are not in any way intended to limit the scope of the invention as claimed.

Example 1

Gel formulation containing calcipotriol and betamethasone

To produce 1 kg of gel formulation, 30 g of hydrogenated castor oil was melted together with 749 g of heptamethylnonane at 85-90°C and cooled with homogenisation to about 60°C. The mixture was then cooled to 25-30°C with stirring. 643 mg of betamethasone dipropionate was suspended in 50 g of heptamethylnonane and added to the homogenised gel base. 52.2 mg of calcipotriol hydrate or 50 mg of calcipotriol was dissolved in 170 g polyoxypropylene-15-stearyl ether and added to the mixture of the other ingredients, and

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the formulation was homogenised to ensure a homogenous distribution of the active components. The resulting gel formulation was stable when stored at 40°C for 3 months, indicating a shelf life of at least 2 years at room temperature. The stability figures are shown in the tables 1 and 2 below.

Table 1

Start 5°C/1month		40°C 1 month		40°C 3 months	
BDP % FOS	Calcipotri. % FOS	BDP % FOS	Calcipotri. % FOS	BDP % FOS	Calcipotri. % FOS
0.23	1.59	0.91	1.52	1.02	1.33
BDP Kvant.	Calcipotri. Kvant.	BDP Kvant.	Calcipotri. Kvant.	BDP Kvant.	Calcipotri. Kvant.
		0.634	50.16	0.642	50.0

Table 2

Start 5°C/1month		40°C 1 month		40°C 3 months	
BDP % FOS	Calcipotri. % Epi	BDP % FOS	Calcipotri. % Epi	BDP % FOS	Calcipotri. % Epi
0.23	0.62	0.91	0.66	1.02	0.8

1 g of the lotion contains:

betamethasone (as dipropionate: 0.643 mg)	0.5 mg
calcipotriol (as hydrate: 52.2 µg)	50 µg
polyoxypropylene-15-stearyl ether (Arlamol® E)	170 mg
hydrogenated castor oil	30 mg
heptanethylnonane (Arlamol® HD)	to make 1 g

CLAIMS

1. A pharmaceutical gel composition for application on skin, said composition comprising at least one vitamin D or vitamin D analogue and at least one corticosteroid, said composition further comprising a viscosity-increasing excipient in an amount resulting in a viscosity which, on the one hand, is sufficient to substantially prevent the corticosteroid from sedimenting during application and storage of the composition and, on the other hand, is sufficient to facilitate an even distribution of the composition.
2. A composition according to claim 1 which has a viscosity in the range of from about 5 mPa.s to about 500 mPa.s, in particular from about 10 mPa.s to about 250 mPa.s, such as from about 20 mPa.s to about 100 mPa.s.
3. A composition according to claim 1 or 2 comprising a thixotropic gelling agent as the viscosity-increasing excipient.
4. A composition according to claim 3, wherein the thixotropic gelling agent is hydrogenated castor oil.
5. A composition according to claim 1 or 2 comprising a viscosity-increasing excipient which is a wax, e.g. Cera Alba (white wax) or Cera Flava (yellow wax), polyethylene or a microcrystalline wax such as Esma-P®.
6. A composition according to any one of claims 1-5 which is a substantially non-aqueous composition.
7. A composition according to any one of claims 1-6 additionally comprising at least one solvent selected from the group consisting of:
 - (i) compounds of the general formula $R^3(OCH_2C(R^1)H)_xOR^2$ (I) wherein x is in the range of 2-60, R^1 in each of the x units independently is H or CH_3 , R^2 is straight chain or branched C_{1-20} alkyl or benzoyl, and R^3 is H or phenylcarbonyloxy;
 - (ii) di-(straight or branched)- C_{4-10} alkyl esters of C_4 - C_8 dicarboxylic acids;
 - (iii) straight or branched C_{12-18} -alkyl benzoates;
 - (iv) straight or branched C_{2-4} -alkyl esters of straight or branched C_{10-18} -alkanoic or -alkenoic acids;
 - (v) propylenglycol diesters with C_{8-14} -alkanoic acids; and
 - (vi) branched primary C_{18-24} alkanols.

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8. A composition according to claim 7, wherein said solvent is selected from compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) wherein R^1 , x , and R^2 are as defined in claim 8, and mixtures thereof.
- 5 9. A composition according to claim 7, wherein R^1 is CH_3 .
10. A composition according to claim 8, wherein said solvent is polyoxypropylene-15-stearyl ether.
- 10 11. A composition according to any one of claims 1-10, wherein said vitamin D analogue is selected from the group consisting of seocalcitol; calcipotriol; calcitriol; tacalcitol, maxacalcitol; paricalcitol; falecalcitriol; $1\alpha,24S$ -dihydroxy-vitamin D₂; and 1(S),3(R)-dihydroxy-20(R)-[[(3-(2-hydroxy-2-propyl)-phenyl)-methoxy]-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene, as well as mixtures thereof.
- 15 12. A composition according to any one of claims 1-11, wherein said vitamin D analogue is selected from the group consisting of calcipotriol, calcitriol, tacalcitol, maxacalcitol, and 1(S),3(R)-dihydroxy-20(R)-[[(3-(2-hydroxy-2-propyl)-phenyl)-methoxy]-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene, as well as mixtures thereof.
- 20 13. A composition according to any one of claims 1-12, wherein the vitamin D analogue is effective against psoriasis and related conditions in humans.
- 25 14. A composition according to claim 15, wherein said vitamin D analogue is calcipotriol or its hydrate.
- 30 15. A composition according to any one of claims 1-14, wherein said corticosteroid is selected from the group consisting of betamethasone, clobetasol, clobetasone, desoximethasone, diflucortolon, diflorasone, fluocinonid, flumethasone, fluocinolol, fluticasone, fluprednidene, halcinonide, hydrocortisone, momethasone, triamcinolon, and pharmaceutically acceptable esters and acetonides as well as mixtures thereof.
- 35 16. A composition according to claim 15 wherein said esters or acetonides are selected from the group consisting of 17-valerate, 17-propionate, 17,21-dipropionate, acetonide, acetonide-21-N-benzoyl-2-methyl- β -alaninate, acetonide-21-(3,3-dimethylbutyrate), and 17-butyrate.

17. A composition according to any one of claims 1-16 containing 0.001-0.25mg/g or ml of said vitamin D analogue and 0.05-2 mg/g or ml of said corticosteroid, in particular 0.1-1.5 mg/g or ml of said corticosteroid.

5 18. A composition according to any one of claims 1-17 essentially comprising the following ingredients (per g of the composition):

	betamethasone (as dipropionate: 0.643 mg)	0.5 mg
	calcipotriol (as hydrate: 52.2 µg)	50 µg
	polyoxypropylene-15-stearyl ether (Arlamol® E)	170 mg
10	hydrogenated castor oil	30 mg
	heptamethylnonane (Arlamol® HD)	to make 1 g

15 19. A composition according to any one of claims 1-18 which further comprises an anti-fungal agent preferably selected from the group consisting of miconazol, clotrimazol, terbinafin, ciclopirox, bifonazol, nystatin, ketoconazol, econazol, and fluconazol.

20. A composition according to any one of claims 1-19 for application on the scalp.

20 21. A composition according to claim 20, additionally comprising a surfactant.

25 22. A composition according to claim 21, wherein the surfactant is selected from the group consisting of octoxynol-n of formula $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$, wherein n is an integer of from 1 to 70, nonoxynol-n of formula $C_9H_{19}C_6H_4(OCH_2CH_2)_pOH$, wherein p is an integer of from 4 to 40, and a polyoxyethylene C_{12-22} alkyl ether, e.g. polyoxyethylene lauryl ether, polyoxyethylene cetyl ether, polyoxyethylene stearyl ether or polyoxyethylene oleyl ether.

30 23. Use of a composition according to any one of claims 1-22 for the manufacture of a medicament for the topical treatment of psoriasis and related conditions in humans.

24. The use of claim 23 for the manufacture of a medicament for the topical treatment of scalp psoriasis.

35 25. A method of treating psoriasis and related conditions, the method comprising administering to an affected skin area of a patient in need thereof an effective amount of a composition according to any one of claims 1-22.

26. The method of claim 25, wherein said composition is administered once or twice a day.
27. The method of claim 25, wherein said composition is administered to the scalp.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 01/00613

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/107, A61K 31/56, A61K 31/59, A61K 47/30, A61P 17/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PAJ, WPI DATA, EMBASE, CA DATA, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0064450 A1 (LEO PHARMACEUTICAL PRODUCTS LTD.), 2 November 2000 (02.11.00), see the abstract and examples 1 and 3 --	1
Y	EP 0471872 A1 (BRISTOL-MYERS SQUIBB COMPANY), 26 February 1992 (26.02.92), claim 15 --	1
Y	US 4610978 A (DIKSTEIN ET AL), 9 Sept 1986 (09.09.86), page 3, line 23 - line 26, claims 18-21 --	1

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 March 2002

Date of mailing of the international search report

03. 04 2002

N Name and mailing address of the International Searching Authority
European Patent Office P.B. 5818 Patenlaan 2
E NL-2280 HV Rijswijk
Tel(+31-70)340-2040, Tx 31 651 epo nl,
Fax(+31-70)340-3016

Authorized officer

Ingrid Fallenius/BS
Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 01/00613

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5185150 A (DE LUCA ET AL), 9 February 1993 (09.02.93), column 11, line 1 - line 58, and the claims --	1
Y	WO 9414453 A1 (LEO PHARMACEUTICAL PRODUCTS LTD.), 7 July 1994 (07.07.94), see the examples and claims 6-9 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK01/00613

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25-27
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK01/00613

Claims 25-27 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

28/01/02

International application No.
PCT/DK 01/00613

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
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				IL	68196 A	29/11/90
US	5185150	A	09/02/93	AT	123409 T	15/06/95
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WO	9414453	A1	07/07/94	AU	678800 B	12/06/97
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				CA	2150827 A	07/07/94
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